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Case Report

# Dilated cardiomyopathy may develop in patients with *Aspergillus* infection

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ABSTRACT

Dilated cardiomyopathy (DCM) is a syndrome characterized by cardiac enlargement and impaired systolic function of one or both ventricles. *Aspergillus* has been reported to cause endocarditis, myocarditis, pericarditis, mediastinitis, septic thrombophlebitis, and infections of aortic grafts. However, to our knowledge, this is the first case of DCM that might have resulted from *Aspergillus terreus* infection. Physicians should be aware that DCM may develop in aspergillus infection.



## 1. Case report

A 74-year-old man with progressive dyspnea presented at our hospital on 5 September, 2006. He was referred by a local doctor for further examination of abnormal shadow on chest imaging study. There was no history of allergy, previous major illness, or risk factors for immunodeficiency. He had worked in a metal factory for twenty years and had a smoking history of 50 pack-year. The white cell count was 10,200 per cubic millimeter, with 72 percent neutrophils, 13 percent lymphocytes, 13 percent monocytes, and 2 percent eosinophils. Serum C-reactive protein showed an elevation to 12.16 mg/dl. The values for liver and renal functions were normal and serum fasting glucose level was normal. Serum CEA and CYFRA were normal. Serum β-D glucan increased to 41.0 pg/ml. Serum *Aspergillus* antigen was negative, and the antigen was negative in all clinical course. Plain chest radiograph demonstrated hyperlucent and fibrous lung with right lung mass (Fig. 1(a)). Chest computed tomography showed bilateral bullous lung with fibrosis, and the right $B^6$ mass with crescent sign (Fig. 1(b)). Echocardiogram showed only mild left ventricular hypertrophy. Left ventricular ejection fraction slightly decreased to 48.5% and the pressure gradient from tricuspid regurgitation was 24.9 mmHg (Table 1). *Aspergillus terreus* was detected in the sputum and bronchial washing fluid by fiber-optic bronchoscope. We diagnosed chronic necrotizing pulmonary aspergillosis (CNPA) due to *A. terreus* infection occurring in pulmonary fibrosis and we started oral voriconazole of 200 mg per day in our outpatient clinic from 7 September. Serum C-reactive protein decreased 5.76 mg/dl on 20 October.

On 28 December, he complained of severe dyspnea and arterial blood gas analysis showed severe hypoxemia of 59.5 mmHg with nasal prongs at 4 L/min. He was admitted for further examination of dyspnea. On admission, the white cell count was 9600 per cubic millimeter, with 91 percent neutrophils, 5 percent lymphocytes, 4 percent monocytes. Serum C-reactive protein showed an elevation to 13.18 mg/dl. Serum creatinine kinase was normal at 90 IU/l. Serum β-D glucan increased to 43.8 pg/ml (Table 1). Plain chest radiograph demonstrated enlargement of the right $B^6$ mass with cardiomegaly and right interlobar pleural effusion (Fig. 2(a)). Chest computed tomography showed right $B^6$ mass enlargement and a new infiltration in the right middle lobe (Fig. 2(b)). The temperature was 37.1 °C. We diagnosed right middle lobe pneumonia accompanied by congestive heart failure. Intravenous ciprofloxacin and micafungin with oral voriconazole were administered from 28 December. As recovery of respiratory failure was late, we added intravenous furosemide and sivelestat with pulse therapy of methylprednisolone. He recovered from respiratory failure on 17 January 2007. Serum β-D glucan decreased to 29.8 pg/ml. However, serum brain natriuretic peptide (BNP) was high at 538 pg/ml (Table 1). Echocardiogram showed diffuse hypokinesis of the left ventricle and the left ventricular ejection fraction was markedly decreased to 29.0% and these findings were compatible with DCM. The pressure gradient from tricuspid regurgitation was 30.7 mmHg. As he did not have any complaints, he was discharged on oxygen therapy on 23 February.

Thereafter, his clinical condition gradually progressed and the patient was readmitted to our hospital a total of four times. Although the values of serum β-D glucan fluctuated within a relatively small range, the values of BNP showed constantly increasing levels and changed markedly with the state of cardiac failure. The pressure gradient from tricuspid regurgitation changed from

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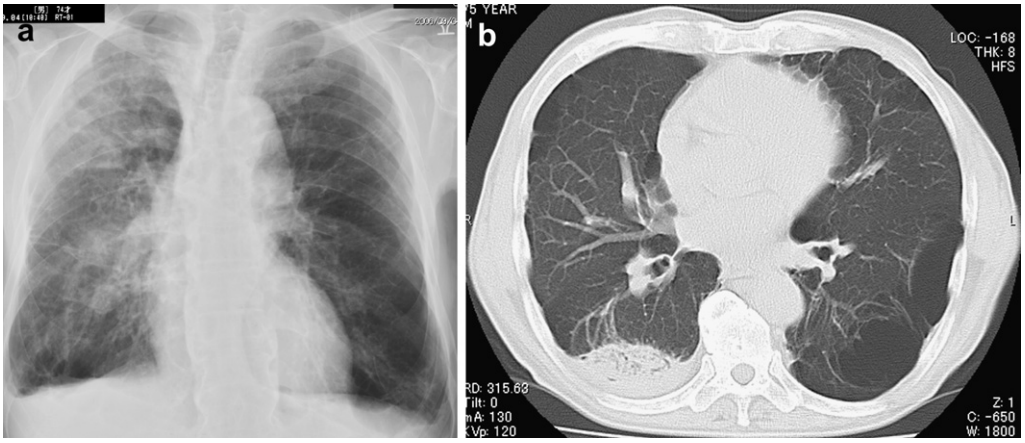


**Fig. 1.** (a) Plain chest radiograph demonstrated hyperlucent and fibrous lung with right lung field mass. (b) Chest computed tomography showed bilateral bullous lung with fibrosis, and the right $B^6$ mass with crescent sign.

30.8 to 46.8 mmHg. Left ventricular ejection fraction changed from 13.7 to 25.0% (Table 1). Coronary arteriogram (CAG) and endomyocardial biopsy of the right ventricle were performed on 29 August. CAG showed intact coronary arteries and the specimen of right ventricle showed moderate myocardial hypertrophy with 25 μm width and many myocytes had degenerated to fat tissue. There were no findings indicating direct invasion of *A. terreus*. We definitely diagnosed DCM.

On 16 November, he was brought to our hospital in a coma by ambulance. The white cell count was 52,000. Serum C-reactive protein showed an elevation to 39.51 mg/dl. Serum creatinine increased to 3.31 mg/dl and serum creatinine kinase increased to1748 IU/l. Serum β-D glucan was 69.0 pg/ml. Serum BNP was 661 pg/ml (Table 1). Methicilin sensitive *Staphylococcus aureus* was detected from sputum. Although biapenem and micafungin were administered, he did not recover. Three days after the admission, he suddenly died probably due to ventricular fibrillation. Autopsy did not permitted.

## 2. Discussion

DCM is a syndrome characterized by cardiac enlargement and impaired systolic function of one or both ventricles. More than half of all patients with a clinical picture of DCM have no identifiable etiology apparent despite rigorous evaluation and are therefore considered to have idiopathic DCM.[1,2] It is likely that this condition represents a common expression of myocardial damage that has been produced by a variety of yet to be identified myocardial insults. Although the cause or causes remain unclear, interest has centered on three possible basic mechanisms of damage[1]: familial and genetic factors,[2] viral myocarditis and other cytotoxic insults, and[3] immunological abnormalities. This patient had no apparent familial linkage to DCM. The reported frequency of evidence of an inflammatory infiltrate in DCM varies widely and undoubtedly depends on the selection of patients and criteria used for diagnosis; using rigorous criteria, only about 15 percent (or less) of patients with DCM show evidence of myocarditis on biopsy.[3] Therefore, we could not completely deny sequela of viral myocarditis by endomyocardial biopsy; at least, endomyocardial biopsy in this case did not demonstrate evidence of inflammatory myocarditis or direct *A. terreus* invasion. Abnormalities of both humoral and cellular immunity have been found in patients with DCM,[4,5] although the findings have not been completely reproducible.[1]

*Aspergillus* has been reported to cause endocarditis, myocarditis, pericarditis, mediastinitis, septic thrombophlebitis, and infections of aortic grafts.[6–10] Most cases occur in solid organ transplant recipients, although the infection has been reported even in immunocompetent patients.[11] In immunocompromised patients, myocarditis occurs as a consequence of a number of disseminated infections. Overt myocarditis is common in disseminated toxoplasmosis, and systemic aspergillosis and candidiasis may also involve the heart.[3,12–17] However, this patient had no immunological defects and did not demonstrate disseminated aspergillus only CNPA due to *A. terreus*.

CNPA is an indolent form of invasive aspergillosis,[18] or "semi-invasive" pulmonary aspergillosis.[19] This infection occurs in mildly immunocompromised host (e.g., diabetes mellitus, low dosage glucocorticoids) and often progresses slowly, usually over a period of several months.[20,21]

Fungal-mediated host cell damage is an important component of fungal virulence and is assumed to facilitate the invasion of host tissues by disrupting host cell membranes, resulting in membrane dysfunction and eventual cell death.[21–23] Phospholipids and proteins represent the major chemical constituents of the host cell envelope. Therefore, enzymes such as phospholipase and proteinase capable of hydrolyzing these proteins are likely to be involved in the host cell-membrane disruption processes. Many fungal pathogens secrete such extracellular proteins, which target the protein or lipid component of host membranes. Thus, secretory proteins have figured prominently among the list of factors

**Table 1**
The changes of serum β-D glucan, BNP and left ventricular EF.

| | 5 Sep. '06 | 28 Dec. '07 | 17 Jan. '07 | 6 Apr. '07 | 7 May '07 | 28 May '07 | 31 July '07 | 8 Aug. '07 | 11 Oct. '07 | 22 Oct. '07 | 16 Nov. '07 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| β-D glucan (pg/ml) | 41.0 | 43.8 | 29.8 | 48.4 | 59.6 | 61.8 | | 38.7 | 41.9 | 39.8 | 69.0 |
| BNP (pg/ml) | | | 538 | 1770 | 484 | 1890 | 540 | 2080 | 1470 | 3730 | 661 |
| CRP (mg/dl) | 12.16 | 13.18 | 9.11 | 12.32 | 8.84 | 18.88 | 11.24 | 4.56 | 13.3 | | 39.52 |
| EF (%) | 48.5 | | 29.0 | 21.2 | | 21.9 | | 25.0 | 13.7 | | 18.8 |
| PG (mmHg) | 24.9 | | 30.7 | 46.3 | | 46.8 | | 38.6 | 43.0 | | 30.8 |

BNP: brain natriuretic peptide, CRP: C-reactive protein, EF: ejection fraction of left ventricle, PG: pressure gradient by tricuspid regurgitation.

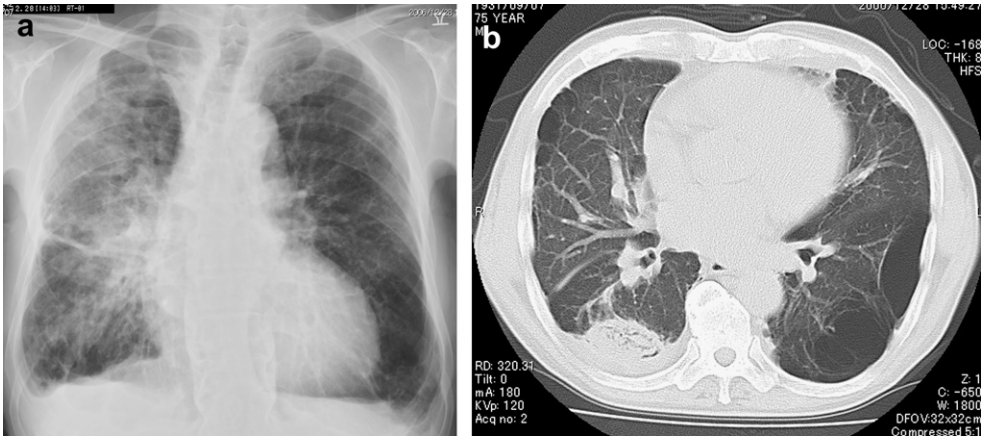


**Fig. 2.** (a) Plain chest radiograph demonstrated enlargement of the right $B^6$ mass with cardiomegaly and right interlobar pleural effusion. (b) Chest computed tomography showed the $B^6$ mass enlargement and a new right middle lobe infiltration.

responsible for fungal virulence. These fungal secretory proteins have been categorized into two main groups; phospholipases, which hydrolyze phospholipid, and proteinases, which hydrolyze peptide bonds.[20] Although the role of these enzymes was not clarified, some elements from *A. terreus* might cause myocardial damage. We should consider the possibility that *A. terreus* infection, not disseminated infection, might result in myocardial damage to DCM.

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